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APPLICATION NUMBER: 019651/S005

PHARMACOLOGY REVIEW(S)

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 062.09.00-CD
Pathology Table 7

Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
MUSCULOSKELETAL SYSTEM:-											
BONE:											
Solitary cyst(s)		(50)	(50)	(50)	(50)	1		(50)	(50)	(50)	(50)
CHONDROSARCOMA (M)										1	
Callus			1	(48)	(50)				(47)	(47)	(49)
JOINT(S):		10	17	14	19			21	21	21	26
No abnormality detected											1
Metastatic site: HISTIOCYTIC SARCOMA (M)										1	1
Focal/multifocal acute/chronic inflammation			1						1		
Focal/multifocal vasculitis			1						1		
Arthropathy		38	27	36	30			21	22		21
Suppurative arthritis											

Figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified.

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
MUSCULOSKELETAL SYSTEM:-											
JOINT(S):											
Focal vascular mineralization		(50)	(48)	(50)	(50)	#	(48)	(47)	(47)	(49)	#
LYMPHOMA (M)		2	1	1	1	#		1	1	1	#
Focal articular cartilage degeneration			1			#					#
Focal/multifocal capsular cyst(s)				1	1	#					#
Focal/multifocal/diffuse synovial inflammation/hyperplasia/congestion		2	3	1	1	#		1	2	1	#
SKELETAL MUSCLE:		(50)	(49)	(50)	(50)	#	(49)	(50)	(50)	(50)	#
No abnormality detected		36	33	31	33	#	38	41	37	40	#
Metastatic site: HISTIOCYTIC SARCOMA (M)			3		1	#	1		1	1	#
Focal/multifocal acute/chronic inflammation		2	4	8	4	#	3	3	4	2	#

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Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0	200	1000	2000	#	0	200	1000	2000	#
		mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
MUSCULOSKELETAL SYSTEM:-											
SKELETAL MUSCLE:											
focal vasculitis		1			2	(50)					
LYMPHOMA (M)		3	2	1	4	(50)					
focal/NOS hematoma				1							
Focal/multifocal myofiber degeneration		7	5	8	9	(50)					
Autolysis			3	1	1						
focal/multifocal myofiber atrophy		1		1							
NERVOUS SYSTEM:-											
BRAIN:											
No abnormality detected		31	34	43	41	(50)					
Metastatic site: HISTIOCYTIC SARCOMA (M)			1								

Figures in brackets represent the number of animals from which this tissue was examined microscopically
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Pathology Table 7
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OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)							
		MALES				FEMALES			
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
NERVOUS SYSTEM:-									
BRAIN:									
Metastatic site: GRANULOCYTIC LEUKEMIA (N)		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Focal/multifocal acute/subacute inflammation		1	2				2	5	
Focal/multifocal vasculitis		3	1			1	1		
Multifocal axonal swelling						1			
Multifocal/NOS spongiosis				1		2	4	3	
Focal/multifocal mineralization		14	10	5	7	3	4	9	3
LYMPHOMA (N)		3	1	1	1	2		3	1
Focal perivascular lymphoid infiltration					1				
Focal hemorrhage									1

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OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
NERVOUS SYSTEM:-											
BRAIN:											
Focal gliosis		(50)	(50)	(50)	(50)	0	(50)	(50)	(50)	(50)	0
Multifocal neuronal atrophy			1			0	1		1		0
SCIATIC NERVE:											
No abnormality detected		(47)	(45)	(47)	(48)	0	(44)	(44)	(46)	(46)	0
Metastatic site: HISTIOCYTIC SARCOMA (M)		30	36	34	38	0	33	31	33	39	0
Metastatic site: GRANULOCYTIC LEUKEMIA (M)			1		1	0	1	1		1	0
Focal/multifocal perineural/MOS subacute inflammation				3		0	2		2		0
Focal/multifocal mineralization				1		0	1				0
LYMPHOMA (M)		1	1	1	1	0	2		3	2	0

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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
NERVOUS SYSTEM:-											
SCIATIC NERVE:											
Multifocal/segmental demyelination		(47)	(45)	(47)	(48)	# (44)	(44)	(46)	(46)	(46)	#
SPINAL CORD:											
Multifocal/segmental demyelination		16	7	10	8	# 7	12	10	5	5	#
No abnormality detected		(50)	(50)	(50)	(50)	# (50)	(49)	(50)	(50)	(50)	#
Metastatic site: HISTIOCYTIC SARCOMA (H)		29	31	44	29	# 39	28	31	32	32	#
Focal/multifocal acute inflammation			2		1	# 1	1	2	1	1	#
Focal/multifocal vasculitis		1	1			# 1	1	1	1	1	#
Focal/multifocal axonal swelling		17	14	5	18	# 6	16	14	12	12	#
Multifocal spongiosis						#	3	1			#
Multifocal malacia			1			#					#
LYMPHOMA (H)		3	1	1	2	# 2	1	1	1	1	#

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)							
		MALES				FEMALES			
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
NERVOUS SYSTEM:									
SPINAL CORD:									
focal/multifocal lymphoid infiltration		(50)	(50)	(50)	(50)	(50)	(49)	(50)	(50)
focal/multifocal hemorrhage			1	1	1			1	1
Multifocal cystic dilation		1							
focal/multifocal neuronal/axonal degeneration		1			1			2	
focal squamous epithelial cyst(s)			1						
Autolysis			1				1		
REPRODUCTIVE SYSTEM - FEMALE:-									
OVARY(IES):									
No abnormality detected						(48)	(47)	(50)	(48)
Metastatic site: HISTIOCYTIC SARCOMA (M)						1	4	4	5
						5	2	5	3

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)					
		MALES			FEMALES		
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	2000 mg/kg
REPRODUCTIVE SYSTEM - FEMALE:-							
OVARY(IES):							
GRANULOSA-THECA CELL TUMOR (N)						(48)	(48)
Focal/multifocal periovarian/NOS acute/chronic inflammation						13	15
Multifocal vasculitis						1	1
One examined						7	7
Multifocal thrombosis						1	7
TERATOMA (B)						1	1
Multifocal/diffuse ceroid/NOS pigmentation						1	2
MYXOMA (B)						1	1
Focal/multifocal mineralization						1	2

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OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - FEMALE:-											
OVARY(IES):											
LYMPHOMA (N)						(48)	(47)	(50)	(48)		
LUTEOMA (B)						5	3	2	4		
LEIOMYOSARCOMA (N)						1		1			
Focal lymphoid infiltration							1				
Multifocal/diffuse stromal/stromal-cell hyperplasia						1	1		1		
Multifocal/diffuse granulosa-cell hyperplasia							1		3		
Focal/multifocal/diffuse epithelial/tubular/papillary hyperplasia						4	1	2	4		
Multifocal hyalinization								1			

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - FEMALE:-											
OVARY(IES):											
Focal/multifocal/NOS hemorrhage/hematoma						#					#
Mass (1): HEMANGIOSARCOMA (H)						# (48)	(47)	(50)	(48)		
Multifocal fibrosis						# 6	4	2	2		
Focal/multifocal/NOS cyst(s)						#		1			
CHORIOCARCINOMA (H)						# 33	29	42	32		
Autolysis						# 1					
Diffuse/NOS atrophy						# 1	2	1			
Multifocal angiectasis						# 7	5				
Focal/multifocal/diffuse amyloidosis						# 1	1	1			
Tubular/NOS ADENOMA (H)						# 11	9	9	8		

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - FEMALE:-											
UTERUS:											
No abnormality detected											
Metastatic site: HISTIOCYTIC SARCOMA (M)											
Primary site: HISTIOCYTIC SARCOMA (M)											
Multifocal/diffuse/MOS Cystic Endometrial Hyperplasia											
Primary site: STROMAL SARCOMA (M)											
Focal endometrial stromal polyp(s)											
Focal/multifocal vasculitis											
Focal/multifocal adenomyosis											
Multifocal hemosiderin pigmentation											
Focal endometrial necrosis											

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - FEMALE:-											
UTERUS:											
Multifocal mineralization						(50)	1	(50)	(50)	(50)	
LYMPHOMA (N)						2	1	2	3		
Multifocal myometrial lymphangiectasia						1		1			
LEIOMYOSARCOMA (M)											
LEIOMYOMA (B)								1			
Focal/multifocal/diffuse endometrial/glandular/luminal/NOS acute/chronic/chronic-active inflammation						6	9	9	8		
Focal stromal cell hyperplasia						1		1			
Multifocal cervical glandular hyperplasia								1			

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - FEMALE:-											
UTERUS:											
focal/multifocal hematoma/endometrial hemorrhage							(50)	(50)	(50)	(50)	
HEMANGIOSARCOMA (H)							2	2	1	1	
focal/multifocal glandular dilatation											1
luminal dilatation						4		4	1	1	
focal endometrial/NOS cyst(s)						1		1	1	2	
Diffuse congestion									2	2	
Autolysis											
focal/multifocal/diffuse endometrial/myometrial angiectasis						2		6	1		
focal/multifocal amyloidosis						2		2	1	2	
						5		1	1		

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		MALES				FEMALES			
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg
REPRODUCTIVE SYSTEM - FEMALE:-									
UTERUS:									
ADENOCARCINOMA (N)									
Focal myometrial abscess(es)									
VAGINA:									
No abnormality detected									
Primary site: HISTIOCYTIC SARCOMA (N)									
Metastatic site: HISTIOCYTIC SARCOMA (N)									
Metastatic site: STROMAL SARCOMA (N)									
Focal/multifocal chronic inflammation									
Focal/multifocal vasculitis									
Focal/multifocal/diffuse/NOS mucoid metaplasia									

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OBSERVATIONS	INCIDENCE OF OBSERVATION (NUMERIC)										
	TREATMENT	MALES				FEMALES					
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	200 mg/kg	1000 mg/kg	2000 mg/kg	#	
REPRODUCTIVE SYSTEM - FEMALE:-											
VAGINA:											
LYMPHOMA (M)						(44)	(43)	(46)	(46)		
Multifocal inflammation						1	3	2	1		
Luminal neutrophilic infiltration							1	1			
Focal/multifocal epithelial hyperplasia						1	2				
Multifocal fibrosis						1		1			
Focal/multifocal cystic/MOS glandular dilatation						2	2	2	2		
Congestion											
Autolysis							1				
ADENOMA (B)						3	2		1		

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
EPIDIDYMS(DES):											
No abnormality detected											
Metastatic site: HISTIOCYTIC SARCOMA (N)											
Metastatic site: GRANULOCYTIC LEUKEMIA (N)											
Aspermia											
Focal/multifocal/diffuse capsular/NOS subacute/chronic inflammation											
Multifocal peri-epididymal acute inflammation											
Focal/multifocal vasculitis											
One examined											
Focal sperm granuloma(s)											

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
EPIDIDYMS(DES):											
Multifocal luminal cellular aggregate(s)		(50)	(50)	(49)	(50)						
Multifocal epithelial vacuolation		2									
Diffuse/NOS oligospermia		10	12	9	8						
Focal/multifocal interstitial/vascular/NOS mineralization		1	1	2	8						
Primary site: MESOTHELIOMA (M)		1									
LYMPHOMA (M)		2	2		2						
Multifocal interstitial fibrosis		1	2	1							
Focal/multifocal ductular dilation		4	6	2	4						
Autolysis			2	2							

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
EPIDIDYMISS(DES):											
Multifocal Interstitial amyloidosis		(50)	(50)	(49)	(50)						
PROSTATE:											
No abnormality detected		9	6	11	12						
Metastatic site: HISTIOCYTIC SARCOMA (M)			4		2						
Metastatic site: GRANULOCYTIC LEUKEMIA (M)			1								
focal/multifocal/diffuse interstitial/NOS acute/subacute/chronic inflammation		34	28	30	27						
focal/multifocal vasculitis		1	3	2	3						
focal/multifocal/diffuse suppurative prostatitis		3	4	5	6						

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		MALES			FEMALES		
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	2000 mg/kg
REPRODUCTIVE SYSTEM - MALE:-							
PROSTATE:							
Focal vascular mineralization							
Metastatic site: MESOTHELIONA (N)		1		1			
LYMPHOMA (N)		3	2	1	2		
Focal epithelial hyperplasia			1				
Multifocal interstitial fibrosis				1			
Focal/multifocal acinar ectasia		6	6	6	2		
Autolysis		1	3	1	2		
SEMINAL VESICLE(S):							
No abnormality detected		(50)	(50)	(50)	(49)		
Metastatic site: HISTIOCYTIC SARCOMA (N)		5	7	3	5		
			2		1		

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		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
SEMINAL VESICLE(S):											
Focal/multifocal/diffuse subacute/chronic inflammation		(50)	(50)	(50)	(49)						
Decreased secretory contents		22	13	14	13						
Focal/multifocal vasculitis		1		2							
Diffuse/NOS acute/NOS seminal vesiculitis			1		1						
LYMPHOMA (H)		2	2	1	2						
Dilatation		35	36	43	41						
Autolysis		2	3	4	3						
Abscess(es)		1									

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
TESTIS(ES):											
No abnormality detected		(50)	(49)	(49)	(49)						
Metastatic site: HISTIOCYTIC SARCOMA (M)		10	13	26	13						
Focal/multifocal interstitial/NOS acute/chronic inflammation		5	3	1	3						
Focal/multifocal vasculitis		2	2		2						
One examined			1	2							
Focal sperm granuloma(ta)		1			2						
Multifocal/diffuse/NOS oligospermia		2	5	5	1						
Focal/multifocal mineralization		10	9	7	14						
Metastatic site: MESOTHELIOMA (M)		1									
LYMPHOMA (M)		2	1		2						

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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
TESTIS(ES):											
Focal/MOS INTERSTITIAL CELL ADENOMA (B)		(50)	(49)	(49)	(49)						
		4			1						
Multifocal tubular epithelial hyperplasia		1									
Multifocal/diffuse interstitial cell hyperplasia		3	2	1	4						
Multifocal interstitial fibrosis		1									
Focal capsular fibrosis				1							
Focal tubular dilation				1							
focal/multifocal/diffuse seminiferous tubular degeneration		34	31	18	30						
Multifocal vascular degeneration			1								
Autolysis			3	3	1						

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7

Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
REPRODUCTIVE SYSTEM - MALE:-											
TESTIS(ES):											
Multifocal interstitial amyloidosis		(50)	(49)	(49)	(49)						
RESPIRATORY SYSTEM:-											
LUNG:											
No abnormality detected		(50)	(50)	(50)	(50)						
Metastatic site: HISTIOCYTIC SARCOMA (M)		10	15	11	8						
Metastatic site: GRANULOCYTIC LEUKEMIA (M)		1	3		1						
Multifocal submucosal glandular acute inflammation		1									
Multifocal vasculitis		2	2	4	2						
Metastatic site: BASOSQUAMOUS CARCINOMA (M)											

figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7

Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
RESPIRATORY SYSTEM:-											
LUNG:											
Focal granuloma(s)					1	1					
Focal bronchiolar mucous accumulation											
Focal/multifocal vascular thrombosis				1		1				1	
Multifocal pneumonia						1					
Multifocal/diffuse perivascular/alveolar edema			1	1	2	2		1	2		
Focal/multifocal vascular/NOS mineralization	1			2				1	4	3	
Primary site: MESOTHELIOMA (M)				1							
LYMPHOMA (M)	3	2	1	1	2	6		5	4	4	

figures in brackets represent the number of animals from which this tissue was examined microscopically
the absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
RESPIRATORY SYSTEM:-											
LUNG:											
Focal/multifocal pleural/interstitial/bronchiolar/alveolar r/nos acute/subacute/chronic/chronic-active/nos inflammation		(50)	(50)	(50)	(50)	# (50)	(49)	(50)	(50)	# (50)	
		16	12	22	16	# 13	14	15	14	#	
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